and added claims is found throughout the specification and claims as originally filed, for example, on pages 5-7.

II. Claim Objections

The Office has objected to claim 1 for reciting improper Markush formatting. Office action, page 2. Applicants have amended claim 1 to recite proper Markush language and respectfully request that the Office withdraw the objection.

The Office has also objected to claim 3 because the disorder "inflammatory" is not grammatically correct. Office action, page 3. Applicants have amended the claim to recite the more grammatically correct phrase, "an inflammatory disorder." Accordingly, Applicants respectfully request that the Office withdraw the rejection.

III. Enablement Rejections

The Office has rejected claims 1-8, under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Office action, page 4. According to the Office, the specification is enabling, "for the inhibition of certain matrix metalloproteinases," but not "for the wide breadth of disorders embraced by the claims." Office Action, page 4. In particular, the Office contends that the specification does not provide adequate guidance concerning the identity of disorders that exhibit enhanced activity of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, and gelatinase A (MMP-2). The Office also contends

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that the specification does not "provide enablement for preventing any disorder." Office Action, page 4 (emphasis in original).

With respect to methods of treating disorders, Applicants respectfully traverse the rejection. However, solely to further the prosecution of this application, Applicants have amended the claims to recite the particular disorders being treated (*i.e.*, that exhibit enhanced activity of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, and gelatinase A (MMP-2)). The disorders listed in claim 2 have been incorporated into claim 1. Thus, there is no question as to what disorders are encompassed by the scope of the claims.

In traversing the rejection, Applicants note that the relevant inquiry for enablement is whether one of skill in the art could make or use the invention from the disclosure in the specification, coupled with information known in the art, without undue experimentation. *See* M.P.E.P. § 2164.01. The test for undue experimentation, however, does not depend on the amount of experimentation, since a considerable amount is permissible, as long as it is routine. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Moreover, a patent need not teach, and preferably omits what is well known in the art. *See* M.P.E.P. § 2164.01, and cases cited therein.

Applicants contend that one of skill in the art, reading the teaching of the specification and using common skill in the art, would know how to make and use the presently claimed invention (*i.e.*, treating the specifically claimed disorders)

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without undue experimentation. Applicants have specifically recited the particular disorders that exhibit enhanced activity of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, and gelatinase A (MMP-2) and are amenable to treatment via the presently claimed method. The skilled artisan, knowing which specific disorders are being treated, can readily determine the proper dosage amounts and schedules for treatment based on the particular set of symptoms presented by each individual being treated. Nothing more than routine skill is involved in making such determinations. Consequently, Applicants contend that the presently amended method of treatment claims are enabled and request that the Office withdraw the rejection.

With respect to "preventing" disorders, Applicants also traverse this rejection. Following a successful treatment protocol, it is entirely within the skill of the art to continue administering the same drug in order to "prevent" recurrence. A doctor can easily determine if such preventative therapy should be given to a subject. That same doctor can also empirically determine the proper amounts for such continuing preventive therapy. No undue experimentation is required. Accordingly, Applicants contend that claims reciting "prevention" are sufficiently enabled and request that the Office withdraw the rejection.

IV. Indefiniteness Rejections

The Office has rejected claims 1-8, under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Office action, pages 5-6. Specifically,

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the Office contends that the phrase, "disorder . . . wherein the disorder displays enhanced activity . . ." does not adequately identify the class of disorders encompassed by the claim. Office Action, page 5. As noted above for the enablement rejection, the incorporation of specific disorders into the claims affirmatively identifies the disorders displaying enhanced activity of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2). As the presently amended claims definitively recite the particular disorders being treated, Applicants respectfully request that the Office withdraw this rejection.

V. Obviousness Rejection

The Office rejected claims 1-8, under 35 U.S.C.§ 103, as allegedly being unpatentable in view of WO 92/19249 ("Yeda") in view of WO 00/056283 ("Goodrich"). *Office action*, pages 6-9. According to the Office, Yeda describes compositions comprising low molecular weight heparin, and their use in inhibiting the secretion of TNF-α. The Office notes that Yeda uses low molecular weight heparin compositions to treat pathological conditions involving induction of TNF-α. As the Office acknowledges, however, Yeda does not teach or suggest the use of any compositions to inhibit neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2), or to treat disorders exhibiting increased activity of these metalloproteinases.

To account for this deficiency, the Office relies on Goodrich. This publication describes various polymers (*e.g.*, unsaturated carboxylic acids) that

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can be used to inhibit metalloproteinases. Goodrich reports that metalloproteinases may play a role in cancer, heart disease, wound healing, and some other diseases. Goodrich also reports that these MMP-inhibiting polymers may be mixed with one or more additional pharmaceutical agents. Among the many possible additional pharmaceutical agents, Goodrich lists heparin. See page 24, lines 4-9. According to the Office, "Goodrich teaches certain polymer compositions that are effective inhibitors of MMPs... [and] discloses that such compositions can contain heparin." Office Action, page 8. Thus, the Office concludes that it would have been obvious to use Yeda's low molecular weight heparins to treat conditions exhibiting elevated levels of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2), as claimed by Applicants.

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, there must be some reason, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to modify or combine the teachings of the references in the manner proposed by the Office. *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996); M.P.E.P. § 2143. The suggestion or motivation must be found in the prior art, not in Applicant's disclosure. *Id.* And the suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). While a person of ordinary skill in the art may possess the

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requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Moreover, the combination of references must also provide a reasonable expectation of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Additionally, the combination must teach or suggest all the limitations of the claims. M.P.E.P. § 2143.03 (and cases cited therein). Applicants contend that the Office has failed to establish a *prima facie* case of obviousness.

The Combination of Goodrich and Yeda
Does Not Provide a Reasonable Expectation of Success

First, there is no reasonable expectation from the teachings of Yeda and Goodrich suggesting that the use of low molecular weight heparin would successfully inhibit or treat disorders involving neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2). As already noted by the Office, Yeda does not teach or suggest MMP-inhibiting treatments at all. And the Office's reliance on Goodrich does not provide the missing expectation of success, since this reference does not teach the use of heparin to inhibit MMPs. Rather, Goodrich describes heparin as one among many miscellaneous pharmaceutical compounds that can be combined with Goodrich's MMP-inhibiting polymers (*e.g.*, unsaturated carboxylic acids). But it is Goodrich's polymers, not the heparin, that are described as inhibiting MMPs. Thus, these teachings do not provide one of skill in the art with any reasonable expectation

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that using enoxaparin would successfully inhibit or treat conditions associated with increased levels metalloproteinase (MMP) activity. Absent a reasonable expectation of success, Applicants contend that the Office has failed to establish a *prima facie* case of obviousness and respectfully request that the rejection be withdrawn.

The Combination of Goodrich and Yeda
Does Not Teach or Suggest All of the Elements of the Claims

Second, even if Yeda and Goodrich were combined, the resulting combination would not teach all of the elements of the claims. As noted above, Yeda fails to teach or suggest the use of enoxaparin to inhibit or treat disorders involving neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2). The Office relies on Goodrich's teaching concerning heparin to provide the missing elements. But Goodrich does not teach the inhibition of any MMPs using heparin. Rather, Goodrich uses only non-heparin polymers to inhibit MMPs. Goodrich notes that heparin is a pharmaceutical additive, but never even suggests that it is a MMP-inhibiting compound.

Moreover, even if Goodrich did provide a teaching concerning the use of heparin to inhibit MMPs, it would still not teach all of the elements of the present claims because the present claims specifically recite enoxaparin. The present specification indicates that heparin and enoxaparin are structurally distinct and can be distinguished by UV spectroscopy, ^{13}C nuclear magnetic resonance spectrum analysis, and high performance size exclusion chromatography. So

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one skilled in the art would not conclude that a teaching concerning heparin necessarily applies to the use of enoxaparin. For these reasons, the proposed combination of teachings utterly fails to teach all of the claim elements (*i.e.*, the use of enoxaparin to inhibit or treat disorders that exhibit enhanced activity of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2)). Again, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejection be withdrawn.

There is No Motivation to Make the Proposed Combination of Goodrich and Yeda

Third, the Office has pointed to no motivation to combine the teachings in the proposed manner. In an attempt to identify the requisite motivation, the Office states, "A skilled artisan would have been motivated . . . since Goodrich discloses compositions containing heparin . . . that show improved antithrombotic performance as well as double the half-life and higher bioavailability." Office Action, page 8.

This motivation does not appear relevant to the present claims, however, which recite the use of enoxaparin to inhibit metalloproteinases. Goodrich's teachings provide absolutely no motivation to use heparin as a MMP-inhibiting compound. As noted above, Goodrich clearly only teaches the use of non-heparin polymers to inhibit MMPs. While it is possible to add a multitude of other pharmaceutical ingredients, including heparin, to Goodrich's polymers, there is

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absolutely no suggestion that any of those ingredients (and, in particular heparin) contributes to the MMP-inhibiting activity of Goodrich's polymers. Rather, given Goodrich's teachings, one of skill in the art would be left to assume that heparin was being added to Goodrich's polymers to serve as an anti-blood clotting agent, its conventional use of heparin.

Such teachings would not lead the skilled artisan to use heparin to treat conditions exhibiting elevated levels of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2). Moreover, as noted above, the present claims recite enoxaparin, not heparin. Thus, the Office's reliance on Goodrich's teachings concerning heparin as motivation for the proposed combination is even further removed from the reality of the actual claim language.

Finally, Applicants note that a particular aspect of the present invention involves the inhibition of specific metalloproteinases. The present specification indicates that a significant drawback with known MMP-inhibitors is their lack of specificity. The present invention is directed to the use of a enoxaparin to specifically inhibit neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1, or gelatinase A (MMP-2). Neither of the cited prior art publications, alone or in combination, provide a teaching or suggestion that would motivate a skilled artisan to select these particular MMPs as a target for inhibition and treatment and derive the presently claimed invention.

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Lacking the requisite motivation to combine the references, Applicants contend that the Office has failed to establish a proper *prima facie* case of obviousness and respectfully request that the rejection be withdrawn.

SUMMARY

In view of these amendments and remarks, Applicants submit that this case is in condition for allowance and respectfully request reconsideration.

Please grant any extension of time required to enter this Response and charge any additional fees to Deposit Account 06-0916.

Respectfully submitted,

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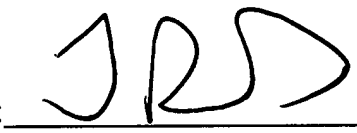
Dated: June 26, 2003

By: 

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